# General

## Guideline Title

Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes.

## Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 45 p. (Technology appraisal guidance; no. 248).

## Guideline Status

This is the current release of the guideline.

# Regulatory Alert

## FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- April 8, 2016 – Metformin-containing Drugs : The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.

# Recommendations

## Major Recommendations

Prolonged-release exenatide in triple therapy regimens (that is, in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in the National Institute of Health and Clinical Excellence (NICE) guideline Type 2 diabetes: the management of type 2 diabetes (clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate (glycated haemoglobin [$HbA_{1c}$] ≥7.5% [59 mmol/mol] or other higher level agreed

with the individual), and the person has:

- A body mass index (BMI) ≥35 kg/$m^2$ in those of European family origin (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight *or*
- A BMI <35 kg/$m^2$, and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related comorbidities.

Treatment with prolonged-release exenatide in a triple therapy regimen should only be continued as described in the NICE guideline Type 2 diabetes: the management of type 2 diabetes (NICE clinical guideline 87); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in $HbA_{1c}$ [11 mmol/mol] and a weight loss of at least 3% of initial body weight at 6 months).

Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulphonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in the NICE guideline Liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal 203); that is, only if:

- The person is intolerant of either metformin or a sulphonylurea, or a treatment with metformin or a sulphonylurea is contraindicated, *and*
- The person is intolerant of thiazolidinediones and dipeptidyl peptidase-4 (DPP-4) inhibitors, or a treatment with thiazolidinediones and DPP-4 inhibitors is contraindicated.

Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described in the NICE guideline Liraglutide for the treatment of type 2 diabetes mellitus (NICE technology appraisal 203); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in $HbA_{1c}$ [11 mmol/mol] at 6 months).

### Clinical Algorithm(s)

A care pathway for diabetes drugs is provided in the Evidence Review (see the "Availability of Companion Documents" field).

## Scope

### Disease/Condition(s)

Type 2 diabetes mellitus

### Guideline Category

Assessment of Therapeutic Effectiveness

Treatment

### Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

### Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

## Guideline Objective(s)

To assess the effectiveness and cost-effectiveness of exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

## Target Population

Adults in England and Wales who have not achieved adequate glycaemic control on maximally tolerated doses of oral antidiabetic therapies

## Interventions and Practices Considered

1. Exenatide prolonged-release suspension for injection in combination with:
    - Metformin and sulphonylurea
    - Metformin and thiazolidinedione
    - Metformin
    - Sulphonylurea
2. Duration of treatment

## Major Outcomes Considered

- Clinical effectiveness
    - Change in glycated haemoglobin ($HbA_{1c}$) level
    - Weight change
    - Adverse events
    - Quality of life
    - Treatment adherence
- Cost-effectiveness

# Methodology

## Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Searches of Unpublished Data

## Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by Warwick Evidence, University of Warwick (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Description of Manufacturer's Search Strategy

The search undertaken by the manufacturer to identify all relevant randomised controlled trials (RCTs) was conducted on 17th January 2011. Seven electronic databases were searched (EMBASE, Medline, Medline In-Process, EBM Reviews [covering the Database of Abstracts of Reviews of Effects (DARE), CENTRAL, Cochrane Methodology Register, Health Technology Assessment (HTA), National Health Service Economic Evaluation Database (NHS EED)], PsycINFO, BIOSIS Previews, Current Contents/All Editions). The Cochrane Database of Systematic Reviews is not listed. Information should have been provided about which databases were searched using the single strategy provided in the manufacturer's submission (MS). The search should have been constructed in a more coherent and systematic way and ideally have been run on each database separately to enable the searches to be reproduced. The search contains several areas of concern. For example, combining step 1 with step 3 (Exp peptides/dt) is inappropriate, because it limits the results to just those from EMBASE. It is unclear how the 171 records kept at step 8 were selected. Other terms for once-weekly such as long-acting OR long acting should have been included at step 10.

Search terms for comparators were not included. A combination of free text and thesaurus terms was applied to the searches to limit them to a particular type of evidence (RCTs). This is not appropriate for databases that focus on the relevant study type (e.g., CENTRAL). Ideally for the larger health databases (e.g., Medline, EMBASE) a validated sensitive RCT search filter such as the Cochrane highly sensitive RCT filter developed in 2008, would have been used. No language restrictions appear to have been applied. In addition to the database search described above, a search of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and Lilly internal database was conducted on 18th January 2011 to identify abstracts or conference proceedings, which was appropriate.

The database and conference proceedings search yielded 64 references. Members of the ERG conducted searches to identify RCTs on long-acting exenatide and liraglutide for a Cochrane review prior to receiving the MS, and do not think any relevant studies have been missed.

See Appendix 8 of the ERG report (see the "Availability of Companion Documents" field) for details of literature search.

Cost-effectiveness

Description of Manufacturer's Search Strategy

The search undertaken by the manufacturer was conducted on 10th February 2011. Three electronic databases were searched (EMBASE, Ovid Medline and EBM Reviews [covering the Cochrane Database of Systematic Reviews, American College of Physicians (ACP) Journal Club, DARE, CENTRAL, Cochrane Methodology Register, HTA, NHS EED]). Two databases listed in the MS template as being required to be included as a minimum, Medline In-Process and EconLIT, do not appear to have been searched. It is unclear which databases were searched using the single strategy provided in the MS. The search should ideally have been run on each database separately to enable the searches to be reproduced. The search contains several areas of concern. For example, it is unclear how the 33 records kept at step 7 were selected. The inclusion of the phrase 'glucagon like peptide receptor agonist' at step 1 is questionable. Either it should not have been included at all or synonyms and alternative terms should also have been included, such as GLP-receptor agonist$, GLP-1 agonist$.

Search terms for comparators were not included. Thesaurus terms were applied to the searches to limit them to a particular type of evidence (cost-effectiveness studies). Sensitive, tested economics filters for PubMed and EMBASE are available (e.g., Centre for Reviews and Dissemination [CRD]'s NHS Economics Evaluation Database Handbook 2007). It would have been more appropriate in a systematic search to have used one of these. By relying on just the database indexing using the relevant MeSH or EMTREE terms, it is possible that relevant papers have been missed. For example, articles containing one or more of the following free text terms in the title or abstract (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$), but that were not indexed with one of the included MeSH or EMTREE thesaurus terms, would not have been retrieved. The use of economic MeSH and EMTREE thesaurus terms in the search used in NHS EED was unwarranted because it is a small database that focuses on economic evaluations. No language restrictions appear to have been applied. No additional sources were searched, but a relevant Lilly-sponsored cost-effectiveness study that was published after the search was conducted was identified.

The database search yielded 126 references, all of which were excluded either because they were not a cost-effectiveness article or because they did not relate to exenatide once-weekly.

See Appendix 8 of the ERG report (see the "Availability of Companion Documents" field) for more information on economic literature search.

## Number of Source Documents

Clinical Effectiveness

Five randomised controlled trials (RCTs) based on the DURATION trial programme were included in the review.

Cost-effectiveness

- No published cost-effectiveness analyses were identified.
- The manufacturer submitted an economic model.

## Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

## Rating Scheme for the Strength of the Evidence

Not applicable

## Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The Evidence Review Group (ERG) report for this technology appraisal was prepared by Warwick Evidence, University of Warwick (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Question 1: Is Once-Weekly Exenatide as Good, or Better Than, Twice Daily Exenatide?

The evidence on this comes from two randomised controlled trials (RCTs) - DURATION 1 and DURATION 5. These were very similar. Full details are given in the industry submission, but in brief:

- The trials were of good quality. Their risk of bias scores were low (see Appendix 1 of the ERG report [see the "Availability of Companion Documents" field]) with the only problem being the inevitable one that blinding of patients is not practical when one arm has twice daily injections and the other has once weekly injections. However the main outcome, glycated haemoglobin ($HbA_{1c}$), is an objective laboratory measure which would not be affected.
- Both compared twice daily with once weekly exenatide in patients with poor glycaemic control ($HbA_{1c}$ baseline mean 8.3%, range 7.1% to 11.0%) on a mixture of treatments. In DURATION 1 15% were on diet and exercise alone, 43% to 46% were on monotherapy (mostly metformin), and 36% to 39% were on dual therapy. In DURATION 5 16 to 21% were on diet and exercise alone, 43% to 50% were on monotherapy (mostly metformin) and 28% to 40% were on dual therapy. Hence these trials do not reflect the real-life position on exenatide long acting (LA) in triple therapy because a minority were on dual therapy.
- The trials were funded by Amylin and Lilly, which were involved in design, and collection, and analysis of data. Some authors were from the manufacturers.

So the patient groups were mostly not relevant to the decision problem (use of exenatide in triple therapy) but the trials are satisfactory for assessing the effectiveness of exenatide LA versus the twice daily (BD) form.

Exenatide LA versus Liraglutide

DURATION 6 compared exenatide LA with liraglutide 1.8 mg daily in 911 patients. Quality of study as assessed by risk of bias table was good, with the only problem being the impracticality of blinding because of different dosing frequencies.

However, the 1.8 mg dose of liraglutide is not recommended by NICE, on cost-effectiveness grounds. So the competitor for once-weekly exenatide is 1.2 mg liraglutide. Unfortunately, DURATION-6 did not include an arm with 1.2 mg liraglutide. The manufacturer therefore commissioned a network meta-analysis to provide an indirect comparison of liraglutide 1.2 mg with exenatide LA.

*The Oxford Outcomes Network Meta-analysis*

This was a good quality review, carried out because there was no head to head trial comparing liraglutide 1.2 mg with exenatide LA. One could have made some minor criticisms, such as that the Jadad scoring system for RCTs is now rather out-dated, and the Cochrane risk of bias method might have been better.

One point of difference from the ERG's analysis is the size of difference in $HbA_{1c}$ between the two liraglutide doses. The ERG's meta-analysis estimated that the difference in $HbA_{1c}$ was 0.10%, the Oxford estimate is 0.17%. Most of the difference is explained by the exclusion of LEAD-3 from the ERG's meta-analysis, on the grounds that LEAD-3 was a monotherapy trial – liraglutide alone versus glimepiride alone. (See Figures 7 and 8 of the ERG report [see the "Availability of Companion Documents" field] for comparison of $HbA_{1c}$ change with or without LEAD-3 trial, respectively.)

The ERG accepted the Oxford Outcomes analysis that liraglutide 1.2 mg and exenatide LA are clinically equivalent.

Exenatide LA Versus Insulin

DURATION 3 compared exenatide LA with glargine insulin in 456 patients previously treated with metformin alone (70%) or metformin + sulphonylurea (30%). Baseline $HbA_{1c}$ was 8.3% and body mass index (BMI) 32.

The study was funded by Lilly and Amylin, the companies were involved in design, data collection and analysis, and four of the seven authors were from the companies.

The summary drew on the Cochrane review of the glucagon-like peptide (GLP)-1 analogues. Of which two members of the ERG were authors.

The end-of-study dose of glargine was 31 units, which was greater than in the LEAD-5 study where the dose only reached 24 units. This suggested more effective titration and a more reliable comparison.

Comparison with Sitagliptin and Pioglitazone

The DURATION 2 trial randomized patients to once-weekly exenatide, pioglitazone or sitagliptin. Trial quality was good (see risk of bias table in Appendix 1 of the ERG report [see the "Availability of Companion Documents" field) but the question addressed is not relevant to UK practice. Firstly, the trial recruited patients on metformin monotherapy. As per the NICE guidelines, the ERG would expect the second drug to be sulphonylurea (or oral alternative such as pioglitazone).

Secondly, in routine care, the ERG would expect patients to be tried first on a (relatively) inexpensive oral drug before an expensive injectable.

A more useful RCT would have been in patients not achieving good control on triple oral therapy. For example, if $HbA_{1c}$ was still too high on metformin + sulphonylurea + a gliptin or pioglitazone, would substituting the gliptin or pioglitazone with exenatide achieve good control, given its somewhat greater glucose-lowering effect? The alternative would be insulin.

See Section 4 of the ERG report (see the "Availability of Companion Documents" field) for more information.

Cost-effectiveness

Manufacturer Submission

The CORE model structure was succinctly summarised within the manufacturer's submission. In brief, the model used patient characteristics such as age, gender, BMI, duration of diabetes, ethnicity, past history of complications (especially cardiovascular disease), and variables such as $HbA_{1c}$, blood pressure, and blood lipids, to estimate long-term outcomes.

The CORE model permits users to adopt one of two modelling approaches:

- Treatment tree, or
- Treatment line

These trees and lines relate to the switching between therapies. In essence, the treatment tree assumes that after a period of time specified by the

user patients fail on one therapy and move onto another. In contrast, the treatment line models an explicit stopping rule based upon an $HbA_{1c}$ cut-off specified by the user, at which point patients fail on one therapy and move onto another.

The manufacturer modelling adopted the treatment tree approach, with the base case in effect assuming that all patients remain on the first treatment for five years, regardless of baseline change in $HbA_{1c}$. After five years all patients were assumed to switch to glargine.

The adoption of the treatment tree approach was in line with the modelling of Technology Appraisal 203. But in response to an ERG clarification question the manufacturer supplied scenario analyses adopting the treatment line approach for the base case analyses.

CORE Model Validation

The CORE model simulations for type 2 diabetes mellitus (T2DM) have been validated for 2nd order validation using epidemiological papers used to construct the CORE model and for 3rd order validation using epidemiological papers not used in the construction of the CORE model. The $R^2$ for these were reportedly 0.975 and 0.875 respectively. The 3rd order validation for T2DM is summarised in Appendix 4 of the ERG report (see the "Availability of Companion Documents" field).

See Section 5 of the ERG report (see the "Availability of Companion Documents" field) for more information.

## Methods Used to Formulate the Recommendations

Expert Consensus

## Description of Methods Used to Formulate the Recommendations

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document' (ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who Is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations

representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

## Rating Scheme for the Strength of the Recommendations

Not applicable

## Cost Analysis

The manufacturer submitted a de novo analysis using the CORE diabetes model to assess the cost-effectiveness of weekly prolonged-release exenatide in treating type 2 diabetes that is inadequately controlled on oral antidiabetic therapy, from a National Health Service (NHS) and personal social services perspective. In the model, weekly prolonged-release exenatide was used as an alternative to liraglutide 1.2 mg in dual therapy regimens where sulphonylureas, thiazolidinediones and dipeptidyl peptidase (DPP-4) inhibitors are not tolerated or are contraindicated, and as part of triple therapy (as an alternative to exenatide twice daily and liraglutide 1.2 mg).

The CORE model consists of 15 Markov submodels that simulate the major macrovascular and microvascular complications of type 2 diabetes. The manufacturer incorporated data from the DURATION-1, DURATION-2, DURATION-3 and DURATION-5 clinical trials and the network meta-analysis in the economic analyses. Because the trials included a mix of background treatments, the manufacturer assumed that the treatment effects were comparable regardless of their place in treatment (dual and triple therapy) and independent of the stage of disease. Comparators were exenatide twice daily, sitagliptin, pioglitazone, insulin glargine, and liraglutide 1.2 mg.

The manufacturer's base-case results showed that weekly prolonged-release exenatide was more costly but was associated with greater life expectancy and more quality-adjusted life years (QALYs) than pioglitazone, sitagliptin and insulin glargine, giving incremental cost-effectiveness ratios (ICERs) of £8624, £6554 and £11,041 per QALY gained respectively. Weekly prolonged-release exenatide dominated exenatide twice daily and liraglutide 1.2 mg because it was associated with greater benefits at a lower cost. Dominance over liraglutide 1.2 mg was the result of a slightly larger predicted reduction in glycated haemoglobin ($HbA_{1c}$) with weekly prolonged-release exenatide and reduced needle costs.

A probabilistic sensitivity analysis presented by the manufacturer showed that, at a threshold of £20,000 per QALY, weekly prolonged-release exenatide had a 99%–100% probability of being cost effective when compared with pioglitazone, sitagliptin, exenatide twice daily and insulin glargine, and an 87.4% probability of being cost effective compared with liraglutide 1.2 mg.

The Evidence Review Group (ERG) considered the direct health-related quality of life impact from changes in body mass index to be a model driver because its exclusion increased the ICER for weekly prolonged-release exenatide when compared with pioglitazone (£17,772 per QALY gained compared with £8624 per QALY gained in the base case) and insulin glargine (£16,605 per QALY gained compared with £11,041 per QALY gained in the base case). The ERG observed that assumed duration of therapy is also a model driver, with cost-effectiveness improving with a shorter duration of therapy before switching. The ERG noted that all the modelling found that weekly prolonged-release exenatide produced similar patient benefits and costs as liraglutide 1.2 mg, although the sensitivity analyses demonstrated that the small net effects cause the analysis to swing from the base case of weekly prolonged-release exenatide dominating liraglutide 1.2 mg to it sometimes being dominated by liraglutide 1.2 mg.

The ERG noted that the model applied lifetime weight changes, which may bias against treatments that increase weight. The ERG undertook sensitivity and scenario analyses on the manufacturer's model to investigate the impact of lifetime maintenance of weight gain on health-related quality of life and the impact of individual clinical effects. A sensitivity analysis in which the disutility associated with increasing weight was only applied for 5 years (that is, before switching treatment to insulin glargine) increased the ICER of weekly prolonged-release exenatide from £8624 per QALY gained to £12,052 per QALY gained for the comparison with pioglitazone and from £11,041 per QALY gained to £12,839 per QALY gained for the comparison of weekly prolonged-release exenatide with insulin glargine.

Summary of Appraisal Committee's Key Conclusions

*Availability and Nature of Evidence*

The Committee noted that the CORE model was also used in NICE technology appraisal guidance 203 and was acceptable, although it noted that these diabetes models are generally rather outdated because they are based on data that are 20 years old. In the absence of more recent data, the Committee concluded, with some reservations, that the CORE model which formed the basis of the manufacturer's submission was acceptable for assessing the cost-effectiveness of weekly prolonged-release exenatide.

*Uncertainties Around and Plausibility of Assumptions and Inputs in the Economic Model*

The assumption that in the base case of the manufacturer's model that treatment with weekly prolonged-release exenatide will last for 5 years before a switch to insulin glargine is not supported by any clinical evidence. The assumption was chosen by the manufacturer for consistency with previous technology appraisals; changes in duration of effect impacted the ICER.

*Incorporation of Health-Related Quality-of-Life Benefits and Utility Values*

The Committee was aware that the model was also used in NICE technology appraisal guidance 203 and included utility values for quality of life and nausea associated with treatment. As a sensitivity analysis, the model included a disutility value associated with injection site reactions.

The Committee considered the main benefit of weekly prolonged-release exenatide to be that patients need fewer injections (weekly versus daily), which reduces the impact of managing type 2 diabetes on the daily lives of patients and carers.

*Are There Specific Groups of People for Whom the Technology Is Particularly Cost Effective?*

No specific groups were identified in which weekly prolonged-release exenatide was particularly cost effective.

*What Are the Key Drivers of Cost-effectiveness?*

The effects of weekly prolonged-release exenatide were driven by changes in $HbA_{1c}$ and weight.

*Most Likely Cost-Effectiveness Estimate (Given as an ICER)*

The Committee noted the ICERs presented in the manufacturer's submission were not specific to the place of weekly prolonged-release exenatide in triple and dual therapy regimens. The Committee did, however, consider on the basis of the ICERs presented in the manufacturer's submission, that weekly prolonged-release exenatide is likely to be cost effective when used in the same place in the treatment pathway as twice daily exenatide and liraglutide 1.2 mg were currently recommended.

See Sections 3 and 4 of the original guideline document for details of the economic analysis provided by the manufacturer, the Evidence Review Group comments, and the Appraisal Committee considerations.

## Method of Guideline Validation

External Peer Review

## Description of Method of Guideline Validation

Consultee organisations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

# Evidence Supporting the Recommendations

## Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated for each recommendation.

The Appraisal Committee considered clinical and cost-effectiveness evidence and a review of this submission by the Evidence Review Group. For clinical effectiveness, five randomised controlled trials (RCTs) were the main source of evidence. For cost-effectiveness, the manufacturer's model was considered.

# Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Appropriate use of exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes

## Potential Harms

The most common adverse drug reactions of exenatide are mainly gastrointestinal (nausea, vomiting, diarrhoea and constipation). Injection site reactions (pruritus, nodules, erythema), hypoglycaemia (with a sulphonylurea), and headache can also occur. Most adverse reactions are mild to moderate in intensity.

For full details of side effects and contraindications, see the summary of product characteristics.

# Contraindications

## Contraindications

For full details of side effects and contraindications, see the summary of product characteristics.

# Qualifying Statements

## Qualifying Statements

- This guidance represents the view of the National Institute for Health and Clinical Excellence (NICE) and was arrived at after careful consideration of the evidence available. Health professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of health professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

# Implementation of the Guideline

## Description of Implementation Strategy

- The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the National Health Service (NHS) in England and Wales on implementing National Institute for Health and Clinical Excellence (NICE) technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must usually provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. When there is no NICE technology appraisal guidance on a drug, treatment or other technology, decisions on funding should be made locally.
- NICE has developed tools to help organisations put this guidance into practice (listed below).
    - A costing statement explaining the resource impact of this guidance
    - Audit support for monitoring local practice

## Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

# Institute of Medicine (IOM) National Healthcare Quality Report Categories

## IOM Care Need

Living with Illness

## IOM Domain

Effectiveness

Patient-centeredness

# Identifying Information and Availability

## Bibliographic Source(s)

National Institute for Health and Clinical Excellence (NICE). Exenatide prolonged-release suspension for injection in combination with oral antidiabetic therapy for the treatment of type 2 diabetes. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 45 p. (Technology appraisal guidance; no. 248).

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Feb

## Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

## Source(s) of Funding

National Institute for Health and Clinical Excellence (NICE)

## Guideline Committee

Appraisal Committee

## Composition of Group That Authored the Guideline

*Committee Members*: Dr Jane Adam (*Chair*), Department of Diagnostic Radiology, St George's Hospital, London; Professor Iain Squire (*Vice-Chair*), Consultant Physician, University Hospitals of Leicester; Professor A E Ades, Professor of Public Health Science, Department of Community Based Medicine, University of Bristol; Dr Jeremy Braybrooke, Consultant Medical Oncologist, University Hospitals Bristol NHS Foundation Trust; Dr Fiona Duncan, Clinical Nurse Specialist, Anaesthetic Department, Blackpool Victoria Hospital, Blackpool; Professor Jonathan Grigg, Professor of Paediatric Respiratory and Environmental Medicine, Barts and the London School of Medicine and Dentistry, Queen Mary University London; Dr Peter Heywood, Consultant Neurologist, Frenchay Hospital, Bristol; Dr Sharon Saint Lamont, Head of Quality and Innovation, North East Strategic Health Authority; Dr Ian Lewin, Consultant Endocrinologist, North Devon District Hospital; Dr Louise Longworth, Reader in Health Economics, HERG, Brunel University; Dr Anne McCune, Consultant Hepatologist, University Hospitals Bristol NHS Foundation Trust; Dr Alec Miners, Lecturer in Health Economics, London School of Hygiene and Tropical Medicine; Ms Pamela Rees, Lay member; Dr Ann Richardson, Lay member; Mr Stephen Sharp, Senior Statistician, MRC Epidemiology Unit; Dr Eldon Spackman, Research Fellow, Centre for Health Economics, University of York; Mr Mike Spencer, Assistant Director Patient Experience, Cardiff and Vale University Health Board; Mr David Thomson, Lay member; Mr William Turner, Consultant Urologist, Addenbrooke's Hospital, Cambridge; Dr Luke Twelves, General Practitioner, Ramsey Health Centre, Cambridgeshire; Dr John Watkins, Clinical Senior Lecturer/Consultant in Public Health Medicine, Cardiff University and National Public Health Service Wales; Dr Anthony S Wierzbicki, Consultant in Metabolic Medicine/Chemical Pathology, Guy's and St Thomas' Hospitals NHS Trust; Dr Olivia Wu, Reader in Health Economics, University of Glasgow

## Financial Disclosures/Conflicts of Interest

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies: An update is available from the National Institute of Health and Clinical Excellence (NICE) Web site .

## Availability of Companion Documents

The following are available:

- Diabetes (type 2) - exenatide (prolonged release). Costing statement. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 6 p. (Technology appraisal 248). Electronic copies: Available from the National Institute for Health and Clinical (NICE) Web site .
- GLP-1 agonists for the treatment of type 2 diabetes. Clinical audit tool. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012. 10 p. (Technology appraisal 248). Electronic copies: Available from the NICE Web site .
- GLP-1 agonists for the treatment of type 2 diabetes. Electronic audit tool. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012. (Technology appraisal 248). Electronic copies: Available from the NICE Web site .
- NICE Pathways. Diabetes. Electronic copies: Available from the NICE Web site .
- Evidence review group report: Long-acting exenatide in the management of type 2 diabetes. Warwick Evidence, University of Warwick; 2011 Aug 19. 122 p. (Technology appraisal 248). Available in PDF from the NICE Web site .

## Patient Resources

The following is available:

- Prolonged-release exenatide injections used with oral treatment for type 2 diabetes. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Feb. 7 p. (Technology appraisal 248). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

## NGC Status

This NGC summary was completed by ECRI Institute on July 3, 2012. This summary was updated by ECRI Institute on April 4, 2014 following the U.S. Food and Drug Administration (FDA) advisory on Rosiglitazone-containing Diabetes Medicines. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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